IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	De Sauvage et al.	Examiner:	RINAUDO, JO ANN S
Serial No.:	10/663,158	Group Art Unit:	1644
Filed:	September 15, 2003	Docket No.:	11669.0123USC1
Conf. No.:	4053	Customer No.:	23552
Title:	TYPE I CYTOKINE RECEPTOR TCCR		

AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action dated November 3, 2005, the date for timely reply being extended three months to expire on May 3, 2006, Applicants submit the following Amendment and Remarks. Entry of the Amendment and reconsideration of the claims is respectfully requested.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims that begins on page 4 of this paper.

Remarks begin on page 8 of this paper.

Amendments to the Specification

Sequence Listing

On July 26, 2004, Applicants submitted a Sequence Listing in response to a Notice of Missing Parts. Applicants respectfully request the specification be amended to include the paper copy of the Sequence Listing submitted on July 26, 2004. Please insert the sequence listing after the Abstract.

Specification

Please replace the paragraph beginning on page 48, line 12 with the following:

The full-length native sequence TCCR genes encoding the polypeptides described in Figure 3 (SEQ ID NO: 1) and Figure 4 (SEQ ID NO:2), or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length TCCR cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of TCCR or TCCR from other species) which have a desired sequence identity to the TCCR polynucleotide sequence encoding the polypeptides disclosed in Figures 3 and 4 (SEQ ID NO:s 1[&] and 2, respectively). Optionally, the length of the probes will be about 20 to 50 bases. The hybridization probes may be derived from regions of the nucleotide sequence encoding the polypeptides of SEQ ID NO:1[&] and 2 wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence TCCR. By way of example, a screening method will comprise isolating the coding region of the TCCR gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such as ^{32}P or ^{35}S, or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the TCCR gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine to which members of such libraries the probe hybridizes. Hybridization techniques are described in further detail in the Examples below. Any EST or

other sequence fragments disclosed herein may similarly be employed as probes, using the methods disclosed herein.

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Withdrawn) A method of enhancing, stimulating or potentiating the differentiation of T-cells into the Th2 subtype instead of the Thl subtype, comprising contacting said T-cells with an effective amount of a TCCR antagonist.

2. (Withdrawn) The method of claim 1, wherein the enhancing, stimulating or occurs in a mammal and the effective amount is a therapeutically effective amount.

3. (Withdrawn) A method of treating a Thl-mediated disease in a mammal comprising administrating to said mammal a therapeutically effective amount of a TCCR polypeptide antagonist.

4. (Withdrawn) The method of claim 3, wherein the Thl-mediated disease is selected from the group consisting of autoimmune inflammatory disease and allograft rejection.

5. (Withdrawn) The method of claim 4, wherein the autoimmune inflammatory disease is selected from the group consisting of allergic encephalomyelitis, multiple sclerosis, insulin-dependent diabetes mellitus, autoimmune uveoretinitis, inflammatory bowel disease and autoimmune thyroid disease.

6. (Withdrawn) The method of claim 3, wherein the antagonist is a small molecule.

7. (Withdrawn) The method of claim 3, wherein the antagonist is an antisense oligonucleotide.

8. (Withdrawn) The method of claim 7, wherein the oligonucleotide is RNA.

9. (Withdrawn) The method of claim 7, wherein the oligonucleotide is DNA.

10. (Withdrawn) The method of claim 3, wherein the antagonist is a TCCR variant lacking biological activity.

11. (Withdrawn) The method of claim 3, wherein the antagonist is a monoclonal antibody.

12. (Withdrawn) The method of claim 11 wherein the antibody has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues.

13. (Withdrawn) The method of claim 3 wherein the antagonist is an antibody fragment or a single-chain antibody.

14. (Withdrawn) The method of claim 3 wherein the antagonist is a TCCR ligand.

15. (Currently Amended) A method of ~~preventing,~~ inhibiting or attenuating ~~the~~ differentiation of T-cells into ~~the~~ a Th2 subtype, comprising ~~the administration of~~ administering to undifferentiated T-cells an effective amount of a TCCR polypeptide or agonist thereof, wherein said polypeptide or agonist induces a TCCR-mediated response.

16. (Currently Amended) The method of claim 15, wherein the ~~preventing,~~ inhibiting or attenuating occurs in a mammal and the effective amount is a therapeutically effective amount.

17. (Withdrawn) A method of treating a Th2-mediated disease in a mammal comprising ~~the~~ administration to said mammal a therapeutically effective amount of a TCCR polypeptide or agonist.

18. (Withdrawn) The method of claim 17, wherein the Th2-mediated disease is selected from the group consisting of: infectious diseases and allergic disorders.

19. (Withdrawn) The method of claim 18, wherein the infectious disease is selected from the group consisting of: *Leishmania major*, *Mycobacterium leprae*, *Candida albicans*, *Toxoplasma gonadi*, respiratory syncytial virus and human immunodeficiency virus

20. (Withdrawn) The method of claim 18, wherein allergic disorder is selected form the group consisting of: asthma, allergic rhinitis, atopic dermatitis and vernal conjunctivitis.

21. (Withdrawn) The method of claim 15, wherein the agonist is a small molecule.

22. (Withdrawn) The method of claim 15, wherein the agonist is a TCCR variant having biological activity.

23. (Amended) The method of claim ~~15~~ 35, wherein the ~~agonist~~ antibody is a monoclonal antibody.

24. (Currently amended) The method of claim 35 ~~23~~, wherein the antibody is a humanized antibody ~~has nonhuman complementarity determining region (CDR) residues and human framework region (FR) residues~~.

25. (Currently amended) The method of claim ~~15~~ 35, wherein the ~~agonist is an~~ antibody fragment is a Fab, Fab', F(ab'), Fv, single-chain antibody, or a diabody.

26. (Withdrawn) The method of claim 15, wherein the agonist is a stable TCCR ECD.

27. (Withdrawn) A method for determining the presence of a TCCR polypeptide in a cell, comprising exposing the cell to an anti-TCCR antibody and measuring binding of the antibody to the cell, wherein binding of the antibody to the cell is indicative of the presence of TCCR polypeptide.

28. (Withdrawn) A method of diagnosing a Thl-mediated or Th2-mediated disease in a mammal, comprising detecting the level of expression of a gene encoding a TCCR polypeptide (a) in a test sample of tissue cells obtained from the mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a lower expression level in the test sample as compared to the control sample indicates the presence of a Th2-mediated disorder and a higher expression level in the test sample as compared to the control sample indicates the presence of a Th1-mediated disorder.

29. (Withdrawn) A method for identifying a compound capable of inhibiting the expression of a TCCR polypeptide comprising contacting a candidate compound with the polypeptide under conditions and for a time sufficient to allow these two components to interact.

30. (Withdrawn) The method of claim 29, wherein the candidate compound is immobilized on a solid support.

31. (Withdrawn) The method of claim 30, wherein the non-immobilized component carries a detectable label.

32. (Withdrawn) A method for identifying a compound capable of inhibiting a biological activity of a TCCR polypeptide comprising contacting a candidate compound with the polypeptide under conditions and for a time sufficient to allow these two component to interact.

33. (Withdrawn) The method of claim 32, wherein the candidate compound is immobilized on a solid support.

34. (Withdrawn) The method of claim 33, wherein the non-immobilized component carries a detectable label.

35. (New) The method of claim 15, wherein said agonist is an antibody or a fragment thereof that binds SEQ ID NO: 1 or 2.

REMARKS

Claims 1-35 are pending. Claims 1-14, 17-22, and 26-34 are withdrawn from consideration, as drawn to a non-elected invention. Claims 15-16 are linking claims.

Claims 15, 16, and 23-25 are newly amended. New claim 35 is added by this Amendment. Support for the amendment and new claims is found in the specification as filed, for example at page 27, lines 28-31, page 3 lines 15-20, and Examples 3 and 12. No new matter is added. Entry of the amendment and consideration of the amended claims is respectfully requested.

1. Restriction

In the prior response to the Examiner's seventeen-way restriction requirement, Applicant's elected Group X, drawn to a method for inhibiting or attenuating the differentiation of Tcells by administering a TCCR agonist, wherein the agonist is an antibody (including monoclonal, humanized, and antibody fragments and diabodies). Generic claims 15 (agonist) and 16 (in a mammal) are linking claims.

2. SEQ ID NOs: 1 and 2:

The Examiner objected to the specification at page 48, line 12, because of incorrect reference to peptide sequences SEQ ID NOs: 1 and 2 as nucleic acid sequences. The specification has been amended to correctly identify SEQ ID NOs: 1 and 2 as peptide sequences encoded by the TCCR genes. Removal of this objection is requested.

3. Enablement under 35 U.S.C. § 112, first paragraph:

Claims 15, 16, and 23-25 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleged the specification fails to provide guidance for using agonist TCCR antibodies in a method of preventing, inhibiting, or attenuating the differentiation of T-cells into the Th2 subtype in a mammal. Applicants respectfully traverse the rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent specification coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The Office Action alleges that the most relevant factors to consider in determining whether the experimentation is undue include: (1) the amount of direction or guidance provided in the specification; (2) the working examples or lack thereof; and (3) the amount experimentation required to enable one skilled in the art to practice the invention.

a. The Specification Enables the Claimed Invention

The Examiner acknowledges in the Office Action that data provided in the specification demonstrates TCCR-/- mice show a greater Th2-mediated response than wild type mice expressing TCCR. Additionally, the Examiner acknowledges incubation of CD4+ cells obtained from TCCR-/- mice demonstrated a diminished Th1-mediated response and an enhanced Th2-mediated response as compared to cells obtained from wild-type mice expressing TCCR. These data demonstrate that in the absence of TCCR receptor activation, an exacerbated Th2 response is induced, evidenced both by Th2-mediated immune response and by production of Th2 cytokines from T cells obtained from TCCR-/- mice. In contrast to the induced Th2 response, TCCR deficient mice and cells obtained from such mice exhibited a reduced Th1 response. Reduced levels of Th1 cytokine production by T cells obtained from TCCR-/- mice, decreased total serum IgG2a, reduced titers or IgG2a in response to *in vivo* challenge with ovalbumin, and the inability to mount a Th1 response to bacterial infection fully demonstrate reduced development of Th1 cells in TCCR-/- mice. Applicants respectfully submit that these data provide guidance to one skilled in the art about the role of TCCR receptor activation in the mediation of T cell differentiation into Th1 and Th2 cells, and this guidance is consistent with the claimed invention.

The Examiner asserts differentiation of Tcells into Th2 subtype is induced by IL-4, and that it is unclear how an agonist of TCCR may inhibit differentiation of Tcells into Th2 cells if other cytokines are involved. Applicants respectfully disagree. As discussed in the specification and diagramed in Figure 2, numerous cytokines are involved in the activation, differentiation,

and immune-mediated responses of Tcells. Development of Th2 cells is mediated by IL-4, and that of Th1 cells by IL-12. The instant application describes a role for activation of the receptor TCCR in this process.

The data provided in the Examples demonstrates inhibition of Th1 cytokine production and mediated responses contrasted with exacerbation of Th2 cytokines and responses in TCCR-/- animals. For example, Applicants disclose in the specification that cytokines produced by Th1 and Th2 cells each inhibit the other, and demonstrate in the examples that the lack of TCCR signaling results in the inability of differentiated Tcells to produce Th1 cytokines, whereas Th2 cytokines are enhanced (Ex. 12).

These data suggest that replacement of TCCR signaling with a TCCR agonist will alleviate the exacerbated Th2 response and restore the diminished Th1 response.

The Examiner's attention is drawn to the Applicant's later published research article and copending U.S. Patent Application Serial No: 11/275,181 that confirm the action of an agonist of TCCR (IL-27) to bias T cell development away from a Th2 subtype and toward a Th1 subtype. Notably, the *Lucas* paper concludes that the TCCR agonist (IL-27) functions "in a paracrine manner to establish IL-12 responsiveness of early developing Th cells, and consequently contributes to bias the T cell response toward a Th1 outcome." (Lucas et.al., 2003, *PNAS* 100:15047-15042) This paper further establishes a mechanism of IL-27/TCCR action, reporting IL-27/TCCR signaling induces TBet, a required factor for Th1 differentiation, and importantly, IL-27/TCCR signaling suppresses the "master switch," GATA-3, to inhibit Th2 differentiation and response.

Applicants respectfully submit the effect of TCCR signaling via an agonist on Th cell differentiation demonstrated by the specification is clearly demonstrated in the specification. Based on *in vivo* and *in vitro* data provided, activation of TCCR receptor signaling would reasonably be expected to promote Th1 cells and inhibit Th2 cells as claimed. No undue experimentation would be required to make and use an agonist of the known receptor, TCCR to effect TCCR signaling and induce results that are predictable from the evidence provided. Accordingly, removal of the enablement rejection is respectfully requested.

b. Preventing

The Examiner objects to the term "preventing" in the claims. Without acquiescing to the rejection and solely to expedite prosecution, claims 15 and 16 have been amended to delete this term from the claims that now recite "inhibiting or attenuating differentiation".

c. TCCR Sequences

The Examiner asserts that the specification fails to provide sufficient guidance for all possible TCCR monoclonal antibodies because the specification only provides the sequences for two TCCR polypeptides.

To clarify that the claimed antibody agonists bind the TCCR polypeptide, new claim 35 recites agonist antibodies and fragments thereof that bind a sequence of SEQ ID NO: 1 or 2. Removal of this rejection is requested.

d. Antibody Fragments

The Examiner suggests the term "antibody fragment" as defined includes non-binding Fc fragments. As discussed above, to clarify the claimed antibody agonist binds TCCR, new claim 35 recites agonist "antibodies and fragments thereof" that bind SEQ ID NO: 1 or 2. Removal of this rejection is respectfully requested.

e. Agonists

The Examiner further asserts that the specification fails to provide sufficient guidance to support all TCCR agonists, citing the definition of "agonist" provided in the specification. Claim 15 has been amended to clarify that the claimed agonist activates the TCCR receptor and thereby induces a TCCR-mediated response. As disclosed in the specification, since TCCR is a receptor, it is a protein that binds another protein to cause a response. Agonists of the receptor therefore include molecules that bind and activate the receptor, including polypeptides, antibodies, small molecules, and the like.

The instant claims have been restricted to methods administering a TCCR polypeptide or agonist antibody or antibody fragments thereof that bind TCCR polypeptide of SEQ ID NO: 1 or 2. Removal of this rejection is requested.

f. Humanized Antibodies

The Examiner has objected to the phrase "non-human CDRs" in Claim 24. Claim 24 has been amended to clarify the claimed antibodies are "humanized antibodies" of claim 35. Humanized antibodies are described, for example, in the definition beginning on page 29. Removal of this rejection is requested.

4. Written Description under 35 U.S.C. § 112, first paragraph

a. Preventing

Claims 15, 16, and 23-25 were rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to contain sufficient written description in the specification for a method of "preventing" differentiation of T-cells into the Th2 subtype. As discussed above, claims 15 and 16 have been amended to delete the term "preventing" and to recite "inhibiting or attenuating". Removal of this rejection is respectfully requested.

b. Agonist

The Examiner alleges the specification fails to contain sufficient written description of TCCR "agonists". As discussed above for enablement, claim 15 has been amended to clarify that the claimed agonist activates the TCCR receptor to induce a TCCR-mediated response. The instant specification provides adequate written disclosure of the structure of TCCR and its role in the development of Tcells and Tcell responses. Removal of this rejection is requested.

5. Provisional Double Patenting Rejection

Claims 15, 16 and 23-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting in view of U.S. Patent Application No. 10/088,950. As the

rejection is provisional, Applicants will consider filing a Terminal Disclaimer if necessary and upon notice of allowable subject matter.

Conclusion

The claim amendments above are made without prejudice to claim broader subject matter in a later filed application.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

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PATENT TRADEMARK OFFICE

Denise M. Kettelberger
Reg. No. 33,924